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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,469	TACHIBANA, HIROFUMI	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,12-17 and 24-34* is/are pending in the application.

4a) Of the above claim(s) *24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,12-17 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/26/07;6/9/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group A, claims 1, 2, 12-17, 31-34, catechin, and inhibition of cell growth, or cancer cell metastasis in the reply filed on 05/07/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

After review and reconsideration, screening an antibody that binds to the 67 kDa laminin receptor for inhibition of cell growth, or cancer cell metastasis has been rejoined with testing a catechin that binds to the 67 kDa laminin receptor for inhibition of cell growth, or cancer cell metastasis, in view that there is art for the antibody.

Accordingly, claims 1, 2, 12-17, 31-34, screening a catechin, or an antibody that binds to 67 kDa laminin receptor, for testing its inhibition of cell growth, or of cancer cell metastasis, is examined in the instant application.

The embodiments of claims 1, 2, 12-17, 31-34, as drawn to testing compounds other than catechin, such as laminin, or its derived peptide, prion protein, that bind to 67 kDa laminin receptor, are withdrawn from consideration, as being drawn to the non-elected invention. Further, the embodiments of claims 1, 2, 12-17, 31-34, as drawn to testing compounds for a neovascularization-inhibiting effect, a neuroprotective effect, an anti-allergic effect, an anti-arteriosclerotic effect and/or a Creutzfelds-Jakob disease infection-inhibiting effect have been withdrawn from consideration as being drawn to non-elected invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-17 and 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-17 and 33-34 are indefinite, because it is not clear in claims 16 and 33 which compound is referred to. Is it the compound having a galloyl group or a test compound?

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 12-17, 31-34 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2)

the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification discloses that among the tested tea catechins, epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC) and epicatechin (EC), in addition to caffeine and quercitin, only EGCG, EGCG"3Me, and ECG that have in common a galloyl moiety, binds to the 67 kDa laminin receptor on a lung cancer cell line transfected with the laminin receptor, and inhibit growth of said cell line **in vitro** (Examples 1 and 3 on pages 37-39, 40-43). The specification discloses that the cell growth inhibiting effect of EGCG is lost when the cell line was pretreated with an antibody that binds to the 67 kDa laminin receptor (p.41, paragraph before last). The specification discloses that it has been suggested that laminin receptor participates in proliferation and invasion and metastasis of cancer cells (p.2).

1. One cannot predict that, other than an antibody to the 67 kDa laminin receptor, that prevents in vivo lung metastasis, the screened catechin drug that binds to the 67 kDa laminin receptor, including epigallocatechin gallate (EGCG), and epicatechin gallate (ECG) would be effective in **in vivo** cell-growth inhibition or inhibition of cancer cell metastasis**.**

One cannot extrapolate in vitro lung cell killing to in vivo cancer therapy, because: 1) cancer cells in vitro are tested in a different environment than that of in vivo environment, which in vitro environment cannot duplicate that of in vivo environment, thus are not predictably response to the same drug as primary cancer cells in a patient, and 2) cancer therapy is unpredictable.

This is evidenced by a review of the effects of tea polyphenols by Hou et al, 2004, Mutation Res, 555: 3-19, IDS of 04/26/07, which teaches that it is not clear whether some of the anti-cancer effect by these phenols, including epigallocatechin gallate (EGCG), and epigallocatechin (EGC) observed in cell lines occur in vivo (p.5). Hou et al teach that there are major problems in extrapolating results observed in cell lines to animal models: a) The concentration of the test compound used in cell lines are much higher than that observed in the plasma or tissue in experimental animals or human after ingestion of tea or related tea preparation, b) the oxygen partial pressure in a cell culture system is much higher than that of blood or tissue, and that EGCG, an antioxidant, is not stable, with a half life of less than 2 h, although such half-life could be extended several fold, by the addition of superoxide dismutase (p.5), and c) the non-specific binding of EGCG to cellular molecules (p.16). Further, although an antibody to the 67 kDa laminin receptor prevents in vivo lung metastasis, one cannot predict that the screened drugs, including epigallocatechin gallate (EGCG), would be effective in in vivo treating cancer or cancer metastasis, because tea polyphenol such as epigallocatechin gallate (EGCG) has different property than an antibody to the 67 kDa laminin receptor, such as binding specificity and half-life, and the effect of such difference on in vivo cancer killing or inhibition of cancer metastasis is unpredictable. Further, Zips et al, 2005, In vivo, 19: 1-8, who teach that prediction of drug effects in cancer patients **based solely** on **in vitro data is not reliable** and further evaluation in animal tumor systems is essential (p.3, second column, last paragraph). Zips et al teach that despite their importance for drug testing, in vitro methods are beset by pitfalls and inherent limitation (p.3). Zips et al further teach that cells in culture represent an artificial and simplified system, and that unlike in vitro situation, a tumor is a 3-dimension complex consisting

of interacting malignant and non-malignant cells (p.3, second column, last paragraph). Zips et al further teach that vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and this fact consists an important source of of heterogeneity in tumor response to drugs that does not exist in vitro (p.3, second column, last paragraph). Lee et al, 1999, J Immunol, 163: 6292-6300, teach that although in vitro sensitization assays increase melanoma specific CTL reactivity with melanoma peptide, such response is not associated with tumor regression (abstract). Kirkin et al, 1998, APMIS, 106 : 665-679, of record, teach that although several peptides of melanoma associated antigens have been identified as being able to induce CTLs, which could lyse cancer cells in vitro, and in particular peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only **one** of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity (p.666, second column, second paragraph, last 6 lines). Similarly, Kimmel et al, 1987 (J. Neurosurg, 66:161-171, of record), who teach that in vitro assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and cannot duplicate the complex conditions of in vivo therapy. Dermer, 1994 (Bio/Technology, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is

well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, cancer therapy is unpredictable. Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Similarly, Gura, 1997, (Science, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para).

2. Further**, claims 12, 13**, encompass the use of any compound having a galloyl group as a control in the claimed screening method, regardless of the degree of the binding affinity of said compound to the 67 kDa laminin receptor, or its property as an antagonist of the laminin receptor. A screened compound that has a higher affinity than said control, or displaces said control is a drug.

One would not know how to use the screened compounds from the claimed method of claims 12, 13, because there is no correlation between the screened compounds and cell growth inhibition or cancer cell metastasis.

In addition, **claims 14-15, 31-32** encompass a screening method, using a genus of compounds having a galloyl group as a control, wherein said genus of compound has growth-inhibiting effect or inhibits cancer cell metastasis. A screened compound that has a higher

affinity than said control, or displaces said control is a drug, and has a growth-inhibiting effect or inhibits cancer cell metastasis.

Even if epigallocatechin gallate (EGCG) or epicatechin gallate (ECG) were successful in treating lung cancer or inhibiting lung cancer metastasis, one cannot predict that any compound, other than EGCG and ECG, that contains as part of its structure the moiety **galloyl,** is an antagonist ligand of the 67 kDa laminin receptor, and is effective in inducing the anti-cancer effect by inhibiting the 67 kDa laminin receptor.

The specification does not have any data or objective evidence, nor one can predict that the galloyl moiety by itself is sufficient as an antagonist ligand for the 67 kDa laminin receptor, effective in inducing the anti-cancer effect of the 67 kDa laminin receptor, such as displacing the binding of the ligand laminin to its receptor. One cannot predict that EGCG or ECG binds to the laminin receptor via its galloyl moiety, wherein the galloyl moiety is in contact with and binds to the same epitope as that of the antagonist anti-laminin receptor antibody used in the claimed invention, because not any part of a ligand is in contact with and binds to the epitope. For example, the binding site for the 67 kDa laminin receptor consists of only 5 amino acids, the YIGSR peptide, of the laminin ligand (Narumi et al, 1999, Jpn J Cancer Res, 90: 425-431, especially p.429, IDS of 04/26/07). In other words, one **cannot predict whether the galloyl moiety is in contact with and binds to the same epitope bound to the anti-laminin receptor antibody, or it only contributes to the configuration of EGCG, EGCG"3Me, and ECG**, which configuration is necessary for said whole compound having a galloyl moiety to fit into the laminin receptor. The specification only discloses that EGCG, EGCG"3Me, and ECG, that have in common a galloyl moiety, bind to the 67 kDa laminin receptor on a lung cancer cell line

transfected with the laminin receptor, and inhibit growth of said cell line in vitro. The galloyl moiety is **only a structural part of** the whole polyphenol ligand (see structure of different tea polyphenols in figure 1 on page 5, in Hou et al, supra). The specification, however, does not have any data or objective evidence, nor one can predict that the galloyl moiety by itself is sufficient to be recognized by the laminin receptor and displaces its natural ligand, such that the laminin receptor could be inhibited.

Similarly, one cannot predict that other than EGCG, EGCG"3Me, and ECG, there exists a compound that has as part of its structure, the moiety galloyl, has a configuration that would be recognized by the laminin receptor and fit into the receptor structure, and acts as an antagonist, such that the laminin receptor could be inhibited. It is noted that a ligand, whether it is an agonist or antagonist, has to have a certain binding stability, and has to have molecular configuration specificity, for example, a certain configuration for perfect fit into the receptor, like lock and key. In addition, not any catechins bind to and inhibit the laminin receptor, as shown by, for example, the catechins epigallocatechin (EGC) and epicatechin (EC), as disclosed in the specification (p.43).

3. Further, the claims as written encompass a method for screening a compound having cell growth inhibition effect **on any cells, including any cancer cells or any normal cells,** or having inhibition effect on metastasis of any cancer cells**.**

Even if epigallocatechin gallate (EGCG) were successful in treating in vivo lung cancer or inhibiting in vivo lung cancer metastasis, one cannot predict that the screened compounds would have cell growth inhibition effect on any cancer cells, or inhibition effect on metastasis of any cancer cells, because different cancers have different etiology and properties and do not

predictably respond the same way to the same drug. Further, one cannot predict that the screened compounds would have cell growth inhibition effect on any cells, such as any normal cells. Hou et al, supra, teach that adding 100 microMole of EGCG to normal epidermal keratinocytes did not induce caspase-3, a component necessaruy for apoptosis (p.6, second column, last paragraph).

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Narumi et al, 1999, Jpn J Cancer Res, 90: 425-431, IDS of 04/26/07.

Claims 1-2 are as follows:

1. (Original) A method of screening a drug having a cell growth-inhibiting effect, a cancer cell metastasis activity-inhibiting effect, a neovascularization-inhibiting effect, a neuroprotective effect, an anti-allergic effect, an anti-arteriosclerotic effect and/or a Creutzfelds-Jakob disease infection-inhibiting effect, which comprises a step of qualitatively or quantitatively determining the degree of binding of a test compound to a 67 kDa laminin receptor, and, when the test compound binds to the 67 kDa laminin receptor from the test data, then judging that the test compound is a drug having a cell growth-inhibiting effect, or a cancer cell metastasis activity-inhibiting effect, a neovascularization-inhibiting effect, a neuroprotective effect, an anti-allergic effect, an anti-arteriosclerotic effect and/or a Creutzfelds-Jakob disease infection-inhibiting effect.

2. (Original) The screening method as claimed in claim 1, wherein the drug has a cell growth-inhibiting effect, and/or a cancer cell metastasis activity-inhibiting effect.

Narumi et al teach testing of an antibody for its binding to the 67 kDa laminin receptor, and its effect on metastasis of human lung fibrosarcoma cells (abstract, p.425, second column, p.426, second column, p427, first column, paragraph before the results).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 14, 2008
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